Acknowledgment. This work has been supported in part by grants from NSF, the Robert A. Welch Foundation, and the National Center for Supercomputing Applications. J. A. McCammon is the recipient of the G. H. Hitchings Award from the Burroughs Wellcome Fund. T. P. Lybrand is the recipient of a Presidential Young Investigator Award from the NSF. M. H. Mazor is supported by an NIH Traineeship under the Houston Area Molecular Biophysics Training Program.

Hydrolytically Degradable Amino Acid Containing Polymers

Andrea Staubli, Eyal Ron, and Robert Langer*

Contribution from the Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received October 5, 1989*

Abstract: A universal approach to incorporate amino acids into a polymeric backbone via hydrolytically labile bonds is reported. The amino acids were first converted into dicarboxylic acids by derivatization at their amino terminus with trimellitic anhydride and subsequently polymerized via the corresponding mixed anhydride by melt polycondensation in vacuo at elevated temperatures (100–200 °C). The reaction conditions (e.g., reaction time, temperature, and effect of several catalysts) were optimized for both the homopolymers and copolymers with sebacic acid in defined ratios. Polymerizations performed at 180 °C gave, in general, maximal molecular weight after 1–2 h, followed by subsequent gelation of the polymers. Higher molecular weight copolymers (M_w >100000) were obtained with increasing content of sebacic acid, which exhibited low melting points (<100 °C) and good solubility in common organic solvents. Both enhanced degradation (as compared to conventional poly(amino acids)) due to the presence of hydrolytically labile anhydride bonds and improved mechanical strength as a result of the existing imide bonds was observed.

A variety of polymeric structures containing amino acids have been synthesized, principally polypeptides which have been used in structural, immunological, and enzymological studies as well as in biomaterials (e.g., sutures,[1,2,17] skin substitutes,[3,4] drug delivery systems[5]). While the significance of polypeptides is unquestioned, their value in some areas such as biomaterials is frequently limited due to undesirable chemical and physical properties, e.g., their chemical inertness—which leads to mainly enzyme-mediated and possibly irreproducible biodegradation[1,2]—and potential antigenicity. Nonpeptidic analogues have been synthesized by using both side-chain modifications and backbone modifications (e.g., replacement of individual backbone elements[6] or copolymerization of intact polypeptide blocks with other chain sequences[7,8]). Another possibility are poly(amino acids) where intact amino acids are polymerized via their side-chain functionalities by nonpeptidic bonds (such as iminocarbonate or ester bonds, which have been reported to display improved film- and fiber-forming properties[9]) generating structural analogues of conventional poly(amino acids).[10] The latter approach, however, is only applicable to selected amino acids, each of them requiring specifically designed synthesis procedures depending on their side-chain functionalities.

In this report we describe a universal approach to incorporate amino acids into the polymeric backbone via hydrolytically labile anhydride linkages. Previous findings showed that the degradation rates of poly(anhydrides) may range from days to years, depending on the choice of monomer unit.[11] It occurred to us that one of the disadvantages of poly(anhydrides), i.e., their poor mechanical properties, may be eliminated by the integration of either amide linkages, which reinforce the polymer by intermolecular attractive forces (e.g., hydrogen bonding)—or imide bonds, which are known for their excellent mechanical and thermal qualities. Best results were obtained in the latter case where the amino terminus is incorporated into a ring system eliminating any interfering side reactions (as opposed to the amide-containing poly(anhydrides) where the polymer synthesis was limited by possible side reactions of the free remaining electron pair on the secondary amide group, e.g., intramolecular cyclization to form *N*-carboxyanhydrides). The chemical synthesis was conducted in three steps. The amino acids were first converted into diacids by condensation with trimellitic anhydride (in the case of amino acids with reactive side-chain functionalities, conventional protecting groups need to be introduced[12]). These dicarboxylic acid monomers were then converted to their mixed anhydride with acetic acid by heating at reflux in acetic anhydride.[13,18] The isolated and purified prepolymers were then subjected to melt-polycondensation at elevated temperatures in vacuo under nitrogen sweep (Figure 1).

This approach allows the integration of essentially any amino acid into the backbone, creating a new class of polymers which should display both enhanced degradability (due to the presence

Table I. Copolymerization of *N*-Trimellitylimidoglycine (TMA-gly) with Sebacic Acid (SA) in Various Ratios at 180 °C

% TMA-gly	% SA	M_w[a]	M_n	M_w/M_n
16	84	104860	51560	2.03
20	80	61880	37670	1.64
29	71	46256	20412	2.27
40	61	27284	10294	2.65
50	50	15530	4959	3.13
63	37	9105	4806	1.89
70	30	6080	3476	1.75
80	20	3098	2162	1.43
90	10	3050	2765	1.1

[a] Melt polymerized for 2 h.

(1) Dickinson, H. R.; Hiltner, A.; Gibbons, D. F.; Anderson, J. M. *J. Biomed. Mater. Res.* **1981**, *15*, 577.
(2) Dickinson, H. R.; Hiltner, A. *J. Biomed. Mater. Res.* **1981**, *15*, 591.
(3) Aiba, S.; Minoura, N.; Fujiwara, Y. *J. Biomed. Mater. Res.* **1982**, *16*, 181.
(4) Aiba, S.; Minoura, N.; Fujiwara, Y.; Yamada, S.; Nakagawa, T. *Biomaterials* **1985**, *6*, 31.
(5) Kopecek, J. *Biomaterials* **1984**, *5*, 19.
(6) Spatola, A. F. Peptide Backbone Modifications. In *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; pp 268–357.
(7) Vlasov, G. P.; Rudkovskaya, G. D.; Ovsyannikova, L. A. *Makromol. Chem.* **1982**, *183*, 2635.
(8) Kumaki, T.; Sisido, M.; Imanishi, Y. *J. Biomed. Mater. Res.* **1985**, *19*, 785.
(9) Goodman, I.; Rhys, J. A. *Polyesters*; American Elsevier: New York, 1965; Vol. 1.
(10) Kohn, J.; Langer, R. *J. Am. Chem. Soc.* **1987**, *109*, 817.
(11) Leong, K. W.; Brott, B. C.; Langer, R. *J. Biomed. Mater. Res.* **1985**, *19*, 941.
(12) Bodanszky, M.; Bodanszky, A. In *The Practice of Peptide Synthesis*; Springer Verlag: 1984.
(13) Domb, A. J.; Langer, R. *J. Polym. Sci.* **1987**, *25*, 3373.

0002-7863/90/1512-4419$02.50/0

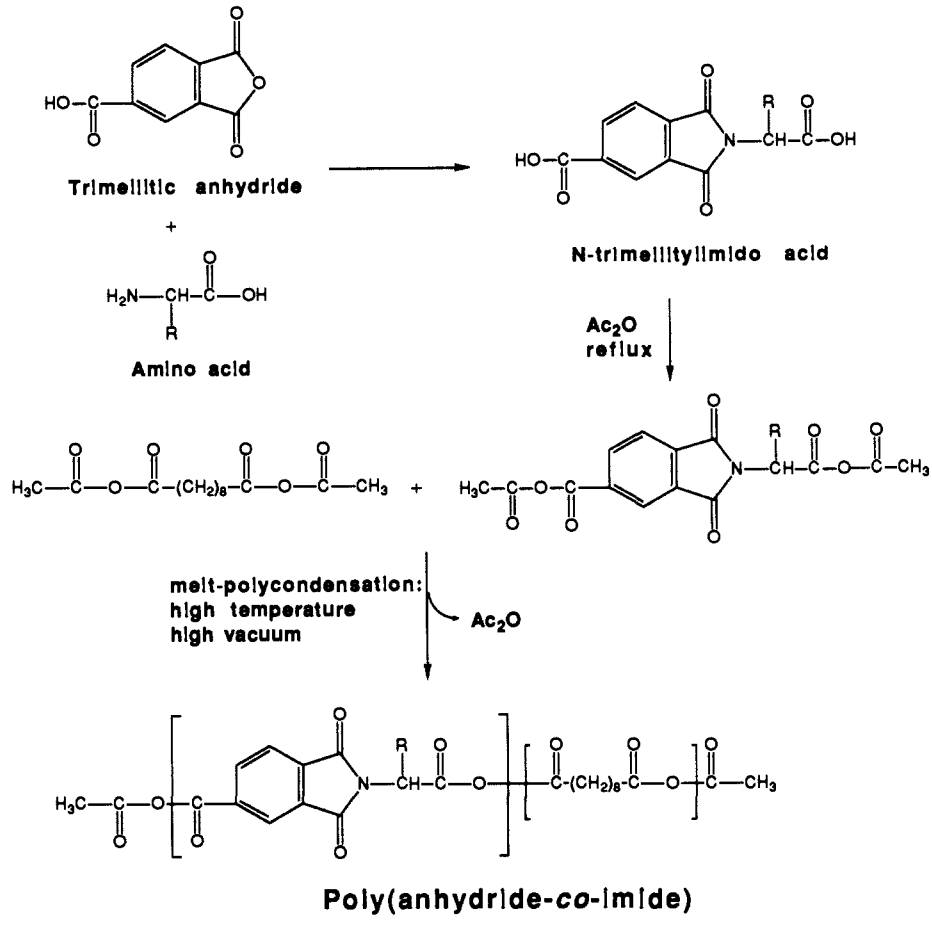

Figure 1. Reaction scheme.

of anhydride bonds) as well as improved mechanical strength (as a result of the existing imide linkages).

Results and Discussion

The preparation of the imide-containing diacids was achieved through direct fusion of a mixture of anhydride and free amino acid (glycine, β-alanine, γ-aminobutyric acid, L-leucine, and L-tyrosine as well as 11-aminoundecanoic acid and 12-aminododecanoic acid), immobilizing the amine terminal of the amino acids in a cyclic imide structure. These diacids were then converted into their corresponding mixed anhydride prepolymer by reflux in acetic anhydride (Figure 1). In the case of heat sensitive amino acids the reaction was performed at lower temperature. Subsequent polymerization of the isolated and purified prepolymers was carried out by melt-polycondensation at elevated temperatures in vacuo. The homopolymers of all *N*-trimellitylimido acids containing naturally occurring amino acids were rigid and brittle with weight average molecular weights below 10000 (as determined by gel permeation chromatography (GPC)). Higher molecular weights were obtained by incorporation of flexible segments into the polymer backbone. This was achieved either by copolymerization of *N*-trimellitylimido acids with an aliphatic spacer (e.g., sebacic acid) in defined ratios (Table I) or by using *N*-trimellitylimido acids containing long aliphatic chains themselves (obtained by condensation of trimellitic anhydride with ω-amino acids such as 11-aminoundecanoic acid). The polymerizations were performed at reaction temperatures between 100 and 200 °C. Dark-colored products which were probably due to either decomposition or cross-linking were observed at reaction temperatures higher than 200 °C. Maximal molecular weight was generally obtained at approximately 180 °C after 1–2 h. Higher molecular weight polymers were also obtained at lower temperatures after prolonged reaction times (up to 24 h) with no decomposition. Several coordination catalysts were tested assuming that complexation of the carbonyl oxygen will enhance the nucleophilic addition involved in the poly(anhydride) formation. Higher molecular weights in shorter time were generally obtained by addition of catalysts such as earth metal oxides and metal salts, whereas alkoxy metals caused a decrease in molecular weight.

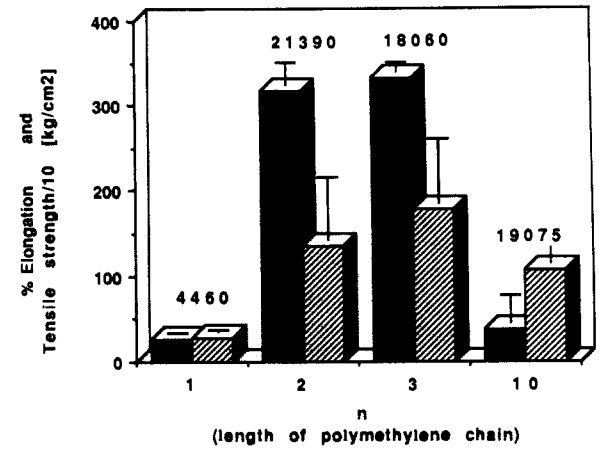

Figure 2. Mechanical properties of selected (TMA-n:SA) (50:50) copolymers (n = 1, 2, 3, 10) (the weight average molecular weights are given above the columns). (■) represents the % elongation, and (□) represents the tensile strength of the specimen (in kg/cm², reduced by a factor of 10).

The physicochemical and mechanical properties of these polymers were dependent on the stoichiometric ratio of the monomers as well as the reaction conditions. Studies were performed on various copolymers, containing either glycine, β-alanine, γ-aminobutyric acid, or 11-aminoundecanoic acid as the amino acid component copolymerized with sebacic acid in various ratios (Figure 2). The reported values are the average of 4-8 measurements for each individual fiber. For each copolymer system optimal mechanical properties (e.g., high tensile strength and/or

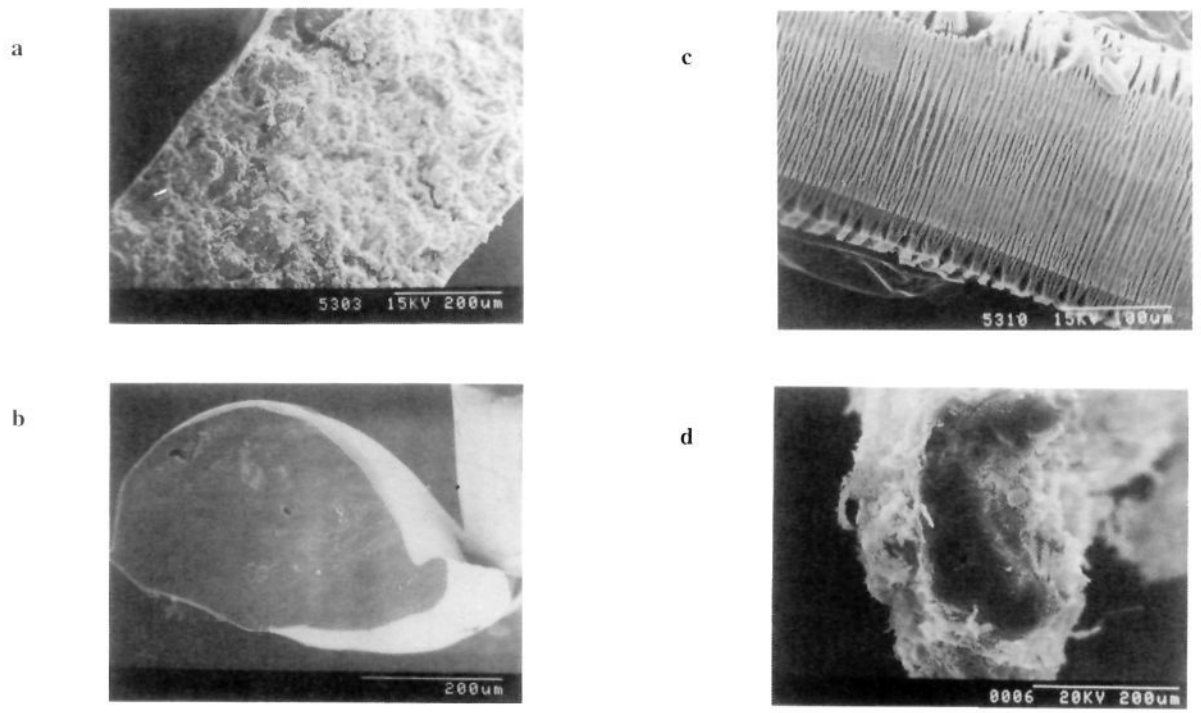

Figure 3. Scanning electron micrographs of (TMA-gly:SA) copolymers: (a) cross section of (TMA-gly:SA) (20:80) as a compression molded device and (b) cross section of (TMA-gly:SA) (50:50) as a meltdrawn fiber. Scanning electron micrographs of copolymers after hydrolytic degradation: (c) cross section of (TMA-gly:SA) (50:50) as a meltdrawn fiber after 2 days of degradation in phosphate buffer (0.1 M, pH 7.4) at 37 °C and (d) cross section of (TMA-10:CPH) (30:70) as a meltdrawn fiber after 1 week of degradation in phosphate buffer (0.1 M, pH 7.4) at 37 °C.

high elasticity) were obtained at a specific ratio of sebacic acid (as the flexible spacer) to rigid imide-containing unit (providing the structural integrity). At very high sebacic acid ratios the relative concentration of the reinforcing imide structure was generally too low to obtain strong fibers (despite the relatively high molecular weight (M_w >50 000) obtained for these copolymers). On the other hand, at low sebacic acid content the copolymers tended to be too rigid and brittle to form flexible fibers. As expected, the optimal monomer ratio shifted to lower sebacic acid content as the chain length of the amino acid component increases. Scanning electron microscopy (SEM) showed that both melt drawn fibers and compression molded devices had a very dense structure (Figure 3a,b).

Increasing solubility in common organic solvents such as chloroform or *N*,*N*-dimethyl formamide was in general observed with a higher content of aliphatic chains. Polymerizations performed at high temperatures (>170 °C), however, induced over time either cross-linking or interlocking of the polymer chains which then became insoluble in common organic solvents.

Both glass transition tempertaures (T_g) of the amorphous polymer fractions and melting temperatures (T_m) of the crystallites were determined by differential scanning calorimetry (DSC). In some cases two closely neighboring peaks for melting temperatures were observed which tended to coalesce after repeated heating, probably representing different crystallite structures. In general, the thermal transition temperatures were significantly reduced—compared to the corresponding homopolymers—probably as a result of disrupted packing of neighboring polymer chains caused by different monomer ratios (Figure 4). The polymers were also analyzed by various spectroscopic methods. Fourier transformed infrared analysis (FTIR) revealed anhydride bands located near 1815, 1775, and 1720 cm^{-1}, which were partially overlapping with the absorptions of the imide bands near 1780 and 1720 cm^{-1}. Additional characteristic imide peaks were observed near 1360 and 720 cm^{-1}. Proton magnetic resonance (^1H NMR) was used for compositional analysis and as a means to determine the stereoregularity of the monomer units by analysis of the different resonances which were observed for the various diads of the two monomers (one of which is asymmetric) (Figure 5).

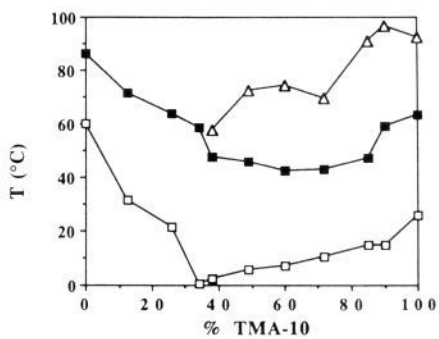

Figure 4. Thermal transition temperatures of (TMA-10:SA) copolymers: (□) represents the glass transition temperatures (T_g) and (■) and (△) represent two melt transitions (T_{m1} and T_{m2}). The second melt transition was only observed for the polymers containing ≥40% TMA-10.

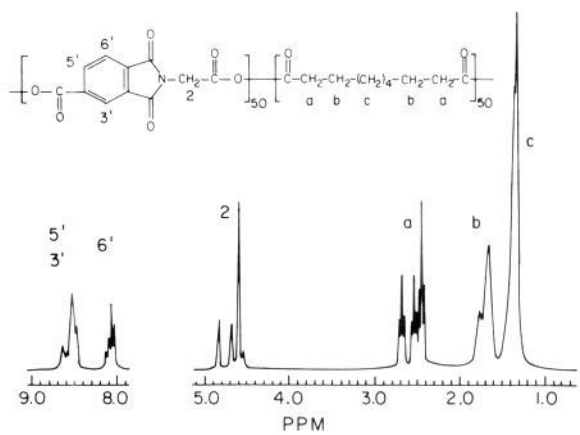

Figure 5. ^1H NMR spectrum of poly(*N*-trimellitylimidoglycine-*co*-sebacic anhydride) (50:50).

Stability in solid state and in chloroform was performed on (TMA-gly:SA) (20:80). The polymer samples of known molecular

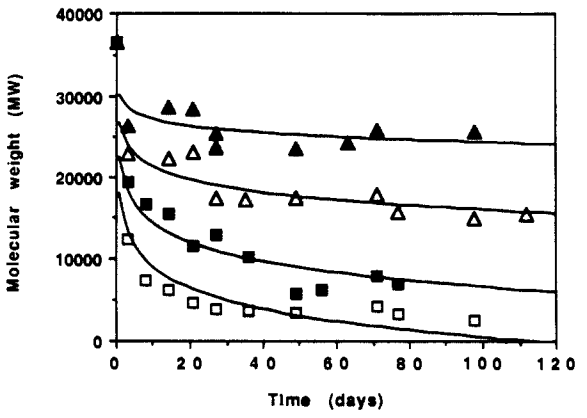

Figure 6. Stability in solid state of (TMA-gly:SA) (20:80) at 37 °C (□), 25 °C (■), 4 °C (△), and −20 °C (▲).

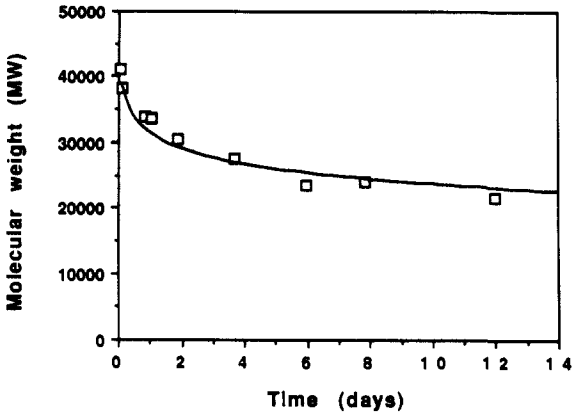

Figure 7. Stability in anhydrous chloroform of (TMA-gly:SA) (20:80) at 25 °C.

weight were stored in solid state under vacuo at −20, 4, 25, and 37 °C, and their molecular weight and composition was followed with time by GPC and both ^{1}H NMR and FTIR spectroscopy. Increasing depolymerization was observed at elevated temperatures (Figure 6). However, polymer samples stored at −20 °C showed almost no decrease in molecular weight and no structural changes (as determined by FTIR and ^{1}H NMR spectroscopy). The stability in solution was determined in anhydrous chloroform (10 mg/mL). The molecular weight decreased very slowly (as determined by GPC) (Figure 7). With time small amounts of a low molecular weight product were observed.

Initial studies on the degradation pattern of copolymers containing glycine as the amino acid component (performed in 0.1 M phosphate buffer, pH 7.4) showed that the degradation rates depended on the monomer ratios as well as on the fabrication method. The more hydrophobic polymers showed generally slow and constant degradation rates. Faster degradation rates were observed with increasing content of aliphatic chains, which is due to the increasing degree of hydrophilicity of the polymer samples with a higher sebacic acid content as well as the differences in crystal structure of the various copolymers. Increasing the sebacic acid ratio in compression-molded devices from 60% to 80% multiplied the degradation rate almost 3-fold (e.g., in the latter case approximately 70% of the polymer was degraded after 6 h). However, compression-molded samples disintegrated earlier than meltcast devices (probably as a result of decreased structural density facilitating diffusion of water molecules through the device). The degradation rates decreased by at least a factor of 12 by using meltcast rather than compression-molded devices of a (TMA-gly:SA) (20:80) copolymer (e.g., after 20 h approximately 50% degradation of the meltcast device was observed). Similar observations were made by using meltdrawn fibers of different molecular composition. Increasing stability was observed in the case of more hydrophobic fibers, which were obtained by replacing the aliphatic chains (sebacic acid) by a substituent of higher

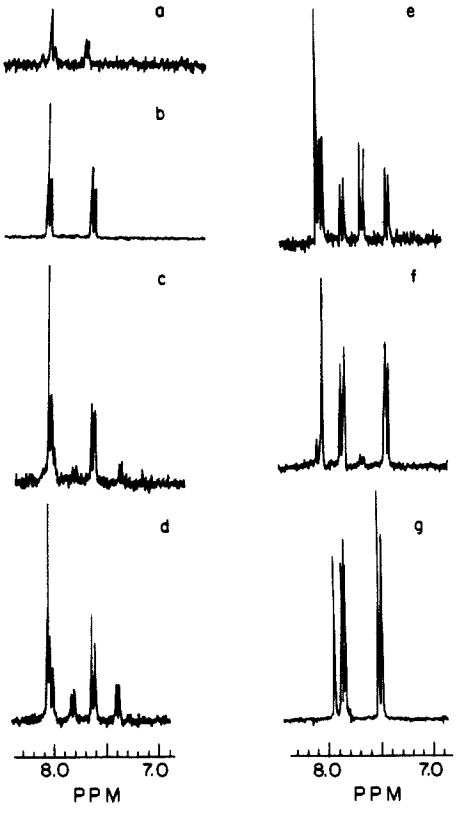

Figure 8. Changes in the ^{1}H NMR spectra of the aromatic protons of a (TMA-gly:SA) (20:80) copolymer during hydrolytic degradation in D_2O/NaOD after (a) 6 h, (b) 2 days 6 h, (c) 10 days 6 h, (d) 20 days, (e) 1 month, and (f) 3 months; (g) represents 1,2,4-benzenetricarboxylic acid (which is the expected degradation product).

aromaticity (1,6-bis(carboxyphenoxy)hexane, CPH). At certain time points during hydrolytic degradation the molecular composition of the harvested polymer samples was analyzed by ^{1}H NMR and FTIR spectroscopy and the erosion zone was examined by SEM (Figure 3c,d).

The postulated degradation pathway (e.g., initial hydrolysis of the anhydride linkages, followed by slow and rate-limiting degradation of the imide bonds to give an intermediate amide structure, and subsequent release of the amino acid[14,15]) was verified by placing a copolymer device in deuterated water at 37 °C and analyzing the solution periodically for degradation products by ^{1}H NMR spectroscopy. The formation of the tetrahedral amido acid intermediate—which is known to have a comparatively high hydrolysis rate due to the presence of a carboxylic acid group in the ortho position with respect to the amide group[14,15]—was analyzed by FTIR spectroscopy, followed by the immediate release of the aromatic tricarboxylic acid and glycine as judged by ^{1}H NMR spectroscopy (Figure 8).

Experimental Section

Materials. Trimellitic anhydride (TMA, Aldrich Chemical Co.) was recrystallized from a mixture of hot toluene and acetic anhydride.

The amino acids used were glycine (Mallinckrodt), β-alanine and γ-aminobutyric acid (Sigma Chemical Co.), L-arginine, L-leucine, and L-lysine (Fluka A.G., Switzerland), L-tyrosine (Chemical Dynamics Corp.), and 11-aminoundecanoic acid and 12-aminododecanoic acid (Aldrich Chemical Co.). Chloroform (gold label, Aldrich Chemical Co.) was purified by passing through basic aluminum oxide (ICN Biokadicals) and stored under inert atmosphere in brown bottles over molecular sieves. All other solvents (gold label, Aldrich Chemical Co.) were used without further purification, unless otherwise specified.

2,2-Dimethyl-2-silapentanesulfonate (DSS) was obtained from Cambridge Isotope Laboratories (CIL, Woburn, MA). 1,6-Bis(carboxy-

(14) Bender, M. L.; Chow, Y.-L.; Chloupek, F. J. Am. Chem. Soc. 1958, 80, 5380.
(15) Korshak, V. V. et al. Polymer Sci. USSR 1972, A14, 2153.

phenoxy)hexane (CPH) was obtained as described elsewhere.[16]

The solid catalysts (Aldrich Chemical Co.) were dried in a vacuum oven at 100 °C for 48 h and sieved manually to less than 50 μ particle size.

Methods. The melting points were determined on a Fisher Johns melting point apparatus.

Optical rotations were measured by a SR6 polarimeter (Polyscience Corp.) at the sodium D line (589 nm) in a 200 mm measuring tube at 22 °C.

Infrared spectroscopy was obtained on a FTIR spectrometer (Perkin-Elmer, MA). The samples were either film cast in chloroform onto NaCl plate or pressed into KBr pellets.

The molecular weights of all the polymer samples were determined on a Perkin-Elmer GPC system (Perkin-Elmer, MA) consisting of the Series 10 pump, the LKB 214 rapid spectral detector at 254 nm wavelength, and the PE 3600 Data station. The samples dissolved in chloroform or a dimethyl formamide/chloroform mixture were eluted through a PL Gel column (Polymer Laboratories, PL-Gel, 30 cm × 1.5 mm, particles 5 μm, mixed bed) at a flow rate of 0.9 mL/min. The molecular weight of the polymers were determined relative to poly(styrene) standards (Polyscience).

Elemental analysis was performed by Galbraith Laboratories (Knoxville, TN).

1H and ^{13}C NMR spectra were obtained on a Varian 250 or 300 MHz and a Varian XL 400 spectrometer, respectively, by using chloroform-d_1, dimethyl sulfoxide-d_6, sodium deuteroxide, or deterium oxide as a solvent and either tetramethylsilane (TMS) and 2,2-dimethyl-2-silapentanesulfonate (DSS), respectively, as internal reference or external standards. The numbering of the structures appears in Figure 5.

Thermal analysis of the polymers was studied on the 7 Series thermal analysis system of Perkin-Elmer. An average sample weight of 5–10 mg was heated at heating rates ranging from 1 to 15 °C/min.

Intrinsic viscosity of the polymer in chloroform solution was measured in a Cannon 75 Ubbelohde viscometer (Cannon, Pennsylvania) at 25 °C.

Scanning electron microscopy was done on an SEM of the type ISI Model DS-130. The samples were dried, mounted on metal stubs, and sputter-coated with gold–palladium (Polaron Instrument E5100).

Tensile properties of meltdrawn fibers were measured by using an Instron (Model 4201) with a strain rate of 4 mm/min. The polymer fibers were drawn directly from the melt, and their dimensions were determined by using either a micrometer and/or individually by SEM. The diameter of the fibers ranged from 0.01 to 0.7 mm, and the lengths of the specimen varied between 1 and 2.5 cm.

Stability studies were performed in solid state and in anhydrous chloroform. The polymer samples were either stored under vacuo at 37, 25, 4, and −20 °C or dissolved in anhydrous chloroform at 25 °C. The molecular weight was followed by GPC with time, and the depolymerization products were analyzed by FTIR and ^1H NMR spectroscopy.

Hydrolytic degradation of compression molded, meltcast, and meltdrawn polymer samples were performed at 37 °C in a sodium phosphate buffer (0.1 M, pH 7.4). Circular disc matrices of defined size (14 mm in diameter, 0.6 mm thick) were prepared by compression molding of the polymer (90–100 mg) on a Carver laboratory press in a stainless steel mold at 10–15 000 psi for 30 min. Meltcast polymer devices (130–150 mg) were formulated in a stainless steel mold of defined dimensions (9.7 mm in diamter, 2.3 mm thick) at 100–150 °C. Polymer fibers were drawn directly from the melt, and their dimensions were determined individually by SEM. The degradation was followed by measuring the UV absorbance at 248 nm of the periodically changed buffer solutions.

Monomer Synthesis. *N*-Trimellitylimidoglycine (TMA-gly). *N*-Trimellitylimidoglycine was prepared by condensation of equimolar amounts of trimellitic anhydride (0.05 mol, 9.61 g) with glycine (0.05 mol, 3.75 g) which were heated at reflux in either *m*-cresol (20 mL) or *N,N'*-dimethyl formamide (20 mL) for 3 h. The solution was cooled, filtered, and concentrated in vacuo. The crude product was extracted several times with anhydrous ethyl ether and then left at −20 °C to crystallize overnight. Alternatively, the filtered solution was added to excess water, causing the diacid monomer to precipitate. The product was then isolated by filtration and recrystallized from water. The yield was in general 75–82%. All other diacid monomers were prepared according to this synthesis procedure, if not stated differently: mp 268 °C; IR (film on NaCl, cm^{-1}) ν(C=O imide) 1780, ν(C=O stretching vibration) 1720, ν(C=O carboxylic acid) 1700, ν(C-N stretching) 1370, ν(C=O imide) 720; ^1H NMR (DMSO-d_6) δ 8.37 (dd, J = 0.9, J = 7.88 Hz, 1 H, $H_{5'}$), 8.25 (br s, 1 H, $H_{3'}$), 8.02 (d, J = 7.8 Hz, 1 H, $H_{6'}$), 4.33 (s, 2 H, H_2). Anal. Calcd for $C_{11}H_7NO_6$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.93; H, 2.87; N, 5.63.

***N*-Trimellitylimido-β-alanine (TMA-β-ala).** Mp 245 °C; IR (film on NaCl, cm^{-1}) ν(C=O imide) 1780, ν(C=O stretching vibration) 1720, ν(C=O carboxylic acid) 1700, ν(C-N stretching) 1370, ν(C=O imide) 720; ^1H NMR (DMSO-d_6) δ 8.31 (dd, J = 7.75 Hz, J = 1.1, 1 H, $H_{5'}$), 8.16 (br s, 1 H, $H_{3'}$), 7.93 (d, J = 7.75 Hz, 1 H, $H_{6'}$), 3.8 (t, J = 7.33 Hz, 2 H, H_3), 2.6 (t, J = 7.38 Hz, 2 H, H_2). Anal. Calcd for $C_{12}H_9NO_6$: C, 54.76; H, 3.45; N, 5.32. Found: C, 54.79; H, 3.49; N, 5.37.

***N*-Trimellitylimido-γ-aminobutyric Acid (TMA-gaba).** Mp 220 °C; IR (film on NaCl, cm^{-1}) ν(C=O imide) 1780, ν(C=O stretching vibration) 1720, ν(C=O carboxylic acid) 1700, ν(C-N stretching) 1370, ν(C=O imide) 725; ^1H NMR (DMSO-d_6) δ 8.3 (dd, J = 1.25, J = 7.83 Hz, 1 H, $H_{5'}$), 8.16 (br s, 1 H, $H_{3'}$), 7.93 (d, J = 7.9 Hz, 1 H, $H_{6'}$), 3.6 (t, J = 6.7 Hz, 2 H, H_4), 2.27 (t, J = 7.2, 2 H, H_2), 1.81 (qi, J = 6.9, 2 H, H_3). Anal. Calcd for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.0; N, 5.05. Found: C, 56.31; H, 3.69; N, 4.7.

***N*-Trimellitylimido-L-tyrosine (TMA-tyr).** Mp 238–240 °C; IR (film on NaCl, cm^{-1}) ν(OH) 3480, ν(C=O imide) 1780, ν(C=O stretching vibration) 1720, ν(C=O carboxylic acid) 1705, ν(C-N stretching) 1375, ν(C=O imide) 730; ^1H NMR (DMSO-d_6) δ 8.33 (dd, J_1 = 1.08 Hz, J_2 = 7.89 Hz, 1 H, $H_{5'}$), 8.19 (br s, 1 H, $H_{3'}$), 7.94 (d, J = 7.8 Hz, 1 H, $H_{6'}$), 6.92 (d, J = 8.36 Hz, 2 H, $H_{5,9}$), 6.53 (d, J = 8.36 Hz, 2 H, $H_{6,8}$), 5.04 (dd, J = 4.88 Hz, J = 11.48 Hz, 1 H, H_2), 3.17–3.4 (m, 2 H, H_3); $[\alpha]_D^{22}$ −216.7° (*c* 2, CH_3OH). Anal. Calcd for $C_{18}H_{13}NO_7$: C, 60.85; H, 3.69; N, 3.94. Found: C, 60.9; H, 3.8; N, 3.94.

***N*-Trimellitylimido-L-leucine (TMA-leu).** Mp 232–234 °C; IR (film on NaCl, cm^{-1}) ν(C=O imide) 1780, ν(C=O stretching vibration) 1725, ν(C=O carboxylic acid) 1690, ν(C-N stretching) 1385, ν(C=O imide) 730; ^1H NMR (DMSO-d_6) δ 8.38 (dd, J = 1.8 Hz, J = 7.8 Hz, 1 H, $H_{5'}$), 8.25 (br s, 1 H, $H_{3'}$), 8.01 (d, J = 8.1 Hz, 1 H, $H_{6'}$), 4.79 (dd, J = 4.35 Hz, J = 12.15 Hz, 1 H, H_2), 2.1–2.2 (ddd, J = 3.9 Hz, J = 12.2 Hz, J = 14.1 Hz, 1 H, $H_{3''}$), 1.79–1.89 (ddd, J = 4.3 Hz, J = 10.2 Hz, J = 14.1 Hz, 1 H, $H_{3'''}$), 1.4–1.5 (m, 1 H, H_4), 0.86 (d, J = 6.3 Hz, 3 H, H_5), 0.84 (d, J = 6.3 Hz, 3 H, H_6); $[\alpha]_D^{22}$ −8.7° (*c* 3, dioxane). Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.02; H, 4.95; N, 4.59. Found: C, 59.29; H, 5.00; N, 4.65.

***N*-Trimellitylimido-11-aminoundecanoic Acid (TMA-10).** Mp 163.5 °C; IR (film on NaCl, cm^{-1}) ν(C=O imide) 1765, ν(C=O carboxylic acid) 1710, ν(C-N stretching) 1400, ν(C=O imide) 750; ^1H NMR (DMSO-d_6) δ 8.3 (dd, J = 1.5 Hz, J = 8.1 Hz, 1 H, $H_{5'}$), 8.18 (br s, 1 H, $H_{3'}$), 7.94 (d, J = 1.5 Hz, J = 7.5 Hz, 1 H, $H_{6'}$), 3.55 (t, J = 6.75 Hz, 2 H, H_{11}), 2.15 (t, J = 7.5 Hz, 2 H, H_2), 1.54 (m, 2 H, H_{10}), 1.44 (m, 2 H, H_3). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.22; H, 6.78; N, 3.85.

Prepolymer Synthesis. *N*-Trimellitylimidoglycine Prepolymer. *N*-Trimellitylimido glycine (0.01 mol, 2.49 g) was added to excess acetic anhydride (50 mL) and heated at reflux under dry nitrogen for 2 h after everything had dissolved. The solution was then filtered, and the excess acetic anhydride was removed by solvent evaporation. The partially crystallized reaction mixture was left at −20 °C to fully crystallize overnight. The product (often a mixture of monomer and dimer) was isolated by filtration, swirled in anhydrous ether for 24 h, filtered, and vacuum dried: IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1810, ν(C=O imide) 1775, ν(C=O stretching vibration) 1720, ν(C-N stretching) 1400, 1365, ν(C=O imide) 720; ^1H NMR ($CDCl_3$) δ 8.54 (br s, 1 H, $H_{3'}$), 8.47 (dd, J = 7.6 Hz, J = 1.4 Hz, 1 H, $H_{5'}$), 8.04 (d, J = 7.9 Hz, 1 H, $H_{6'}$), 4.6 (s, 2 H, H_2), 2.44 (s, 3 H, $H_{2''}$), 2.31 (s, 3 H, $H_{2''}$).

All mixed anhydride prepolymers were prepared by using the synthesis procedure described above (their melting points were all lying below 100 °C).

***N*-Trimellitylimido-β-alanine Prepolymer.** IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1810, ν(C=O imide) 1770, ν(C=O stretching vibration) 1720, ν(C-N stretching) 1390, 1365, ν(C=O imide) 740; ^1H NMR ($CDCl_3$) δ 8.48 (s, 1 H, $H_{3'}$), 8.45 (d, J = 7.5 Hz, 1 H, $H_{5'}$), 7.99 (d, J = 7.5 Hz, 1 H, $H_{6'}$), 4.07 (t, J = 7 Hz, 2 H, H_3), 2.93 (t, J = 7.1 Hz, 2 H, H_2), 2.44 (s, 3 H, $H_{2''}$), 2.25 (s, 3 H, $H_{2''}$).

***N*-Trimellitylimido-γ-aminobutyric Acid Prepolymer.** IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1810, ν(C=O imide) 1770, ν(C=O stretching vibration) 1710, ν(C-N stretching) 1380, ν(C=O imide) 755; ^1H NMR ($CDCl_3$) δ 8.4–8.6 (m, 2 H, $H_{3',5'}$), ca. 8 (m, 1 H, $H_{6'}$), 3.9* (t, H_4, J = 6.4 Hz) and 3.83 (t, H_4, J = 6.5 Hz), 2.78* (t, H_2, J = 7 Hz) and 2.56 (t, H_2, J = 7.1 Hz), 2.44 (s, $H_{2''}$), 2.23 (s, $H_{2''}$), 2–2.2 (m, H_3) (* monomer and dimer).

***N*-Trimellitylimido-L-tyrosine Prepolymer.** IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1820, ν(C=O imide) 1780, 1755, ν(C=O stretching vibration) 1710, ν(C-N stretching) 1380, ν(C=O imide) 740.

***N*-Trimellitylimido-L-leucine Prepolymer.** Oil at room temperature; IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1810, ν(C=O imide) 1770, ν(C=O stretching vibration) 1720, ν(C-N stretching) 1375, ν(C=O imide) 750, 760; ^1H NMR ($CDCl_3$) δ 8.5 (m, 2 H, $H_{3',5'}$), 8.05 (d, J =

(16) Conix, A. *Macromol. Synth.* **1966**, *2*, 95.

(17) Miyamae, T.; Mori, S.; Takeda, Y. U.S. Patent 3,371,069, Feb 27, **1968**.

(18) Gonzalez, J. I.; de Abajo, J.; Gonzalez-Babe, S.; Fontan, J. *Angew. Makromol. Chem.* **1976**, *55*, 85.

7.73, 1 H, $H_{6'}$), 5.07 (dd, J = 4.33 Hz, J = 11.4 Hz, 1 H, H_2), 2.45 (s, 3 H, $H_{2'''}$), ca. 2.4 (m, 1 H, H_3), 2.3 (s, 3 H, $H_{2''}$), ca. 2 (m, 1 H, H_3), ca. 1.5 (m, 1 H, H_4), 0.97 (br t, 6 H, $H_{5,6}$).

N-Trimellitylimido-11-aminoundecanoic acid Prepolymer. IR ($CHCl_3$, cm^{-1}) ν(C=O anhydride) 1805, ν(C=O imide) 1765, ν(C=O stretching vibration) 1710, ν(C-N stretching) 1390, ν(C=O imide) 750; ^1H NMR ($CDCl_3$) δ ca. 8.5 (m, 2 H, $H_{3',5'}$), ca. 8.0 (m, 1 H, $H_{6'}$), 3.72* (m, 2 H, H_{11}), 2.67* (t, J = 7.35 Hz, 2 H, H_2), 2.45* (t, J = 7.35 Hz, 2 H, H_2), 2.4 (s, 3 H, $H_{2'''}$), 2.2 (s, 3 H, $H_{2''}$), 1.7 (m, 4 H, $H_{3,10}$), 1.35 (m, 12 H, H_{4-9}) (* monomer and dimer).

Polymerization. Poly(*N*-trimellitylimidoglycine-*co*-sebacic anhydride). The *N*-trimellitylimidoglycine prepolymer was mixed with sebacic acid prepolymer in a defined ratio (with or without 1-2 mol % of a catalyst) in a Kimax glass tube with a side arm equipped with a capillary nitrogen inlet. The tube was immersed in an oil bath at the selected temperature (100-250 °C). After the prepolymers were melted, high vacuum was applied ($\leq 10^{-1}$ Torr), and the condensation byproduct, acetic anhydride, was collected in a chilled trap. At the end of the reaction the crude polymer was removed from the glass tube and dissolved in anhydrous methylene chloride or chloroform. The solution was filtered and precipitated into excess petroleum ether. The precipitate was collected by filtration, washed with anhydrous ethyl ether, and dried under vacuum at room temperature for 1 h.

All polymers were prepared by using the same synthesis procedure described above. If the polymers were not soluble in methylene chloride, they were purified by stirring in anhydrous ethyl ether for several hours.

The spectral data for poly(*N*-trimellitylimidoglycine-*co*-sebacic anhydride) (22:78) melt polymerized at 150 °C (without any catalyst) are as follows: GPC M_w = 38 783, M_n = 12 277, M_w/M_n = 3.16; ^1H NMR ($CDCl_3$) δ 8.52 (s, $H_{3'}$), 8.48 (d, $H_{5'}$, J = 8 Hz), 8.04 (d, $H_{6'}$, J = 7.8 Hz), 4.59 (s, H_2), 2.67 (t, H_a (SA-TMA), J = 7.3 Hz), 2.53 (t, H_a (SA-Gly), J = 7.3 Hz), 2.44 (t, H_a (SA-SA), J = 7.35 Hz), 1.68 (m, H_b), 1.3 (m, H_c); ^{13}C NMR ($CDCl_3$) δ 169 ($C_{7',8'}$), 168, 165, 162 (C=O, anhydride), 136.3 ($C_{5'}$), 136.1 ($C_{1'}$), 134.9 ($C_{4'}$), 132.4 ($C_{2'}$), 125.1 ($C_{3'}$), 124.1 ($C_{6'}$), 39.8 (C_1), 35.4, 35.2 (C_a), 28.8, 28.7 (C_b), 24 (C_c); IR (KBr, cm^{-1}) 2920, 2850 ν(C-H), 1810 ν(C=O anhydride), 1730 ν(N—C=O imide). Anal. Calcd: C, 63.04; H, 6.95; N, 1.61. Found: C, 62.14; H, 6.71; N, 2.02.

The spectral data for poly(*N*-trimellitylimido-β-alanine-*co*-sebacic anhydride) (16:84) melt polymerized at 120 °C with 2 mol % $Ca(CO_3)_2$ are as follows: GPC M_w = 91 582, M_n = 31 786, M_w/M_n = 2.88; ^1H NMR ($CDCl_3$) δ 8.44 (m, $H_{3',5'}$), 7.98 (d, $H_{6'}$, J = 7.7 Hz), 4.07 (t, H_3, J = 6.88 Hz), 2.93 (t, H_2, J = 6.85 Hz), 2.67 (t, H_a (SA-TMA), J = 7.25 Hz), 2.44 (t, H_a (SA-SA and SA-β-Ala), J = 7.27 Hz), 1.65 (m, H_b), 1.3 (s, H_c); ^{13}C NMR ($CDCl_3$) δ 169.5 ($C_{7',8'}$), 168.7, 168.3, 166.5 (C=O, anhydride), 136.2 ($C_{5'}$), 135.9 ($C_{1'}$), 134.4 ($C_{4'}$), 132.4 ($C_{2'}$), 124.9 ($C_{3'}$), 123.8 ($C_{6'}$), 35.4, 35.1 (C_a), 33.9, 33.5 ($C_{1,2}$), 28.8, 28.6 (C_b), 24 (C_c); IR (KBr, cm^{-1}) 2930, 2860 ν(C-H), 1810 ν(C=O anhydride), 1730 ν(N—C=O imide); mp 65 and 68 °C. Anal. Calcd: C, 63.95; H, 7.53; N, 1.14. Found: C, 62.49; H, 7.28; N, 1.4.

Acknowledgment. We thank Melissa Lucarelli for her laboratory assistance and Dr. Edith Mathiowitz. Financial support was provided by NIH Grant GM26698 and a gift from NOVA Pharmaceuticals.

Supplementary Material Available: Tables of polymerizations performed at various temperatures and with different catalysts, FTIR spectrum of a typical copolymer, and degradation profiles of various copolymers (3 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of All Four Geometric Isomers of Internal 1,3-Butadienes by the Condensation Reaction of Aldehydes with the γ-Trimethylsilyl-Substituted Allylboranes

Kung K. Wang,* Yu Gui Gu, and Chin Liu

Contribution from the Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045. *Received May 12, 1989. Revised Manuscript Received February 2, 1990*

Abstract: Hydroboration of 2-(trimethylsilyl)-2,3-pentadiene or 4-(trimethylsilyl)-2,3-octadiene with 9-borabicyclo[3.3.1]nonane or dicyclohexylborane produced the corresponding γ-trimethylsilyl-substituted allylborane which condensed smoothly with aldehydes to afford, after elimination of hydroxytrimethylsilane by either basic or acidic workup, a variety of internal 1,3-butadienes. Apparently, high diastereoselectivity was obtained during the condensation step and therefore allowed an easy control of the geometry of one of the two resulting double bonds by simply employing either basic or acidic workup conditions to promote the Peterson olefination reaction. The geometry of the other double bond could also be controlled by selecting either 9-borabicyclo[3.3.1]nonane or dicyclohexylborane as the hydroborating agent. Consequently, all four geometric isomers of several representative internal 1,3-dienes were synthesized with high isomeric purity by utilizing different combinations of the hydroborating agents and the workup conditions. The [1,3] sigmatropic rearrangement of γ-trimethylsilyl-substituted allylboranes was studied by ^1H NMR.

Development of new methodologies for the stereoselective synthesis of 1,3-butadienes has been the focus of attention for many years.[1-3] This interest is due in part to their utilities in the Diels-Alder reaction[4] as well as the discovery of many biologically active natural products having the conjugated diene functionality.[1f] One of the recent advances involves the use of palladium-catalyzed cross-coupling of alkenyl organometallics with alkenyl halides or triflates.[1] However, in order to produce high isomeric purity for the resulting 1,3-dienes, the alkenyl reagents with predetermined geometry must be utilized. It is not always an easy task to prepare certain alkenyl reagents with specific geometry. A different approach utilizes the condensation reaction of aldehydes with

(1) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040 and references cited therein. (b) Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329-1332. (c) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972-980. (d) Negishi, E.-i.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1560-1562. (e) Molander, G. A.; Zinke, P. W. *Organometallics* **1986**, *5*, 2161-2162. (f) Björkling, F.; Norin, T.; Unelius, C. R.; Miller, R. B. *J. Org. Chem.* **1987**, *52*, 292-294 and references cited therein. (g) Jabri, N.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr., II* **1983**, 321-331, 332-338.

(2) (a) Liu, C.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 4733-4734. (b) Pearson, W. H.; Lin, K.-C.; Poon, Y.-F. *J. Org. Chem.* **1989**, *54*, 5814-5819. (c) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751-2752. (d) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311-318. (e) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723-730, 731-741 and references cited therein.

(3) (a) Block, E.; Aslam, M.; Eswarakrishnan, V.; Gebreyes, K.; Hutchinson, J.; Iyer, R.; Laffitte, J.-A.; Wall, A. *J. Am. Chem. Soc.* **1986**, *108*, 4568-4580. (b) Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron* **1984**, *40*, 3645-3655. (c) Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron* **1984**, *41*, 867-873. (d) Trost, B. M.; Fortunak, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 2841-2843. (e) Cuvigny, T.; Fabre, J. L.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4319-4322.

0002-7863/90/1512-4424$02.50/0